EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

General framework on managing uncertainties

EMA Extrapolation Workshop

Presented by Kevin Blake 18 May 2016
Scientific Specialist Clinical Pharmacology

An agency of the European Union

Uncertainty in extrapolation

- Inevitably some uncertainties in the exercise – a model considered to work well for a sub-group but less confidence in the predictions for another – may reflect available data
- ? is the uncertainty more than if clinical data based
- Uncertainty associated with model predictions of the impacts of possible decisions √ *mathematics/statistics*
- Uncertainty associated with the general approach through extrapolation concept and planning √ *specific gaps –more general unease*
- Information on uncertainty may not make decision-making easier but to ignore it is to ignore reality

Identification of uncertainties

For an 'identified' uncertainty from the model:

1. Consider it's 'importance' i.e. how critical it's addressing is to establishing the benefit-risk
2. Is there a need for some form of controlled data to provide reassurance that the observed PK/PD similarity translates across into benefit?
   - *How much benefit do we need – efficacy/effectiveness?*
   - *What sort of efficacy endpoint do we need, assuming we already have some PK/PD data – PD/efficacy hybrid e.g. HbA1C*
   - *What might the study look like – clinical trial, observational study*
3. Does this need to be done pre-authorisation?

More general uncertainty

For a less-well defined uncertainty:

1. Again how critical is further understanding of this aspect in the context of an overall positive benefit-risk –are the results potentially going to result in an update to the label?
2. Is there a need for additional data or further analyses to provide reassurance on this aspect of the benefit?
   - *How much benefit do we need - effectiveness?*
   - *What sort of endpoint, assuming we already have an established benefit-risk*
   - *What might the study look like – observational, analysis of existing data, further modelling?*
3. Assumed this can be done post-authorisation?

Experience from similar challenges

- Concept of risk management planning: ability to classify and structure risk and proactively manage/adapt

- Concept of post-authorisation efficacy studies: ability to establish a positive benefit-risk with a ‘full’ marketing authorisation but with need for studies to address well-reasoned scientific uncertainty on an aspect of benefit that are feasible, ethical and lead to interpretable results

Framework:

- Pre-authorisation: alongside the extrapolation component of a regulatory submission, there should be a clear summary of what is generally known on the topic, including a structured assessment of identified uncertainties and a plan to address these to the extent feasible and taking account of the post-marketing setting.
- Post-authorisation: plan to address uncertainties will be amended in light of new data and the marketing authorisation would be amended as appropriate.
- Acknowledged some ‘residual’ uncertainty will remain and may be reflected in RMP

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